CONCISE REVIEW

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Periodontal disease and the metabolic syndrome

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The metabolic syndrome (MetS) is a spectrum of conditions that increase the risk of cardiovascular disease and diabetes mellitus. The components of MetS include dysglycemia, visceral obesity, atherogenic dyslipidemia (elevated triglycerides and low levels of high-density lipoprotein) and hypertension. An association of periodontal disease and MetS has been suggested. This association is believed to be the result of systemic oxidative stress and an exuberant inflammatory response. When examined individually, the components of the MetS that are most closely related to the risk of periodontitis are dysglycemia and obesity, with lesser contributions by atherogenic dyslipidemia and hypertension. Data suggest that the odds of periodontitis increase with the number of MetS components present in an individual. The direction of the relationship between MetS and periodontal disease cannot currently be determined because the majority of studies are cross-sectional. The association between MetS and periodontitis, however, suggests that improved understanding of this association could promote interprofessional practice. Evidence suggests that periodontal therapy can reduce the levels of inflammatory mediators in serum. If this finding is confirmed, periodontal treatment could become part of therapy for MetS. Oral health providers who identify patients at risk for MetS could refer them to a medical provider, and physicians could refer patients to dentists to ensure that patients with MetS receive a dental evaluation and any necessary treatment. These clinical activities would improve both oral and general health outcomes.

Key words: *Periodontitis, metabolic syndrome, dysglycemia*

The metabolic syndrome (MetS) is a spectrum of conditions that place an individual at increased risk for cardiovascular disease (CVD) and type 2 diabetes mellitus (T2DM). These conditions include dysglycemia, visceral obesity, atherogenic dyslipidemia [elevated triglycerides (TG) and low levels of high-density lipoprotein (HDL)] and hypertension. Periodontal disease is a recognised risk factor for the complications of T2DM[1,2], as well as poor metabolic control[3], and has also been associated with increased risk for CVD in cross-sectional studies[4,5]. Research has explored possible associations and aetiological relationships between periodontal disease and MetS. This review aims to provide an overview of the relationship between MetS and periodontal disease.

OVERVIEW OF THE METABOLIC SYNDROME

As noted, MetS is a spectrum of conditions that increase the risk of CVD and T2DM. The most important risk factors for MetS are obesity, physical inactivity and insulin resistance, but aging, hormonal imbalance and genetic predisposition also have a contributing role[6,7]. Similarly to obesity, the prevalence of MetS has increased over the last decade. In the USA, the estimated prevalence of MetS, of 34.7% in 2011–2012[8], represented a slight increase from the 2003–2006 National Health and Nutrition Examination Survey (NHANES) estimate of 34.0%[9]. Over the same time period, the obesity rate increased from 33.4% to 35.3%[10]. Similarly to obesity, the prevalence of MetS increases with age, as 18.3% of 20- to 39-year-old adults had MetS compared with 46.7% of those 60 years of age or older[8]. The development of insulin resistance, a potential consequence of obesity, is a major event in MetS aetiology and has been hypothesised as a link between MetS components[11].

MetS is believed to originate from a pro-inflammatory state, which can occur as a result of the effects of insulin resistance. Insulin resistance is a condition in which insulin is produced by the pancreas, but is not efficiently bound by muscle, fat and liver cells, as a

result of dysfunctional signalling. The outcome is reduced glucose uptake from the bloodstream[12]. Insulin resistance may promote inflammation through a number of mechanisms, including increased free fatty acid concentration and interference with the anti-inflammatory effects of insulin[13].

Insulin resistance is associated with both increasing body mass index (BMI) and increasing waist circumference, each of which reflect increased levels of adiposity and deposition of visceral adipose tissue. Adipocytes and infiltrating macrophages produce cytokines, including tumour necrosis factor-alpha (TNF-α), interleukins (ILs), and other signalling molecules associated with pro-inflammatory activity and insulin resistance[14]. Increased levels of circulating inflammatory mediators (e.g. TNF-α and IL-6) have been identified in individuals with obesity and insulin resistance[11].

Insulin resistance may also be induced by oxidative stress. An imbalance between caloric intake and energy expenditure (i.e. positive energy balance) may result in oxidative stress, which in turn can alter intracellular signalling pathways, ultimately leading to insulin resistance[15]. Systemic oxidative stress is significantly higher in individuals with MetS compared with controls. Advanced glycation end-products (AGEs) are considered as markers of this stress, and, when bound to their receptors (RAGEs), may induce local oxidative damage[15].

Diagnostic criteria for MetS have been suggested by a number of different health organisations. While there are differences between the definitions, all criteria focus on obesity, dyslipidemia, hypertension and dysglycemia:

- The National Cholesterol Education Program's Adult Treatment Panel III (NCEP ATP III) developed the most commonly referenced diagnostic criteria for MetS[16]. The American Heart Association and National Heart, Lung, and Blood Institute (AHA/NHLBI) revised these criteria in 2005[17]. Both criteria define MetS as the presence of three or more conditions from a list of five (*Table 1*), relying on physical measurements more heavily than on clinical judgment
- The International Diabetes Federation (IDF) and the World Health Organization (WHO) established separate diagnostic criteria for MetS (*Table 1*). The IDF definition[18] differs from those of the NCEP ATP III and the AHA/NHLBI in that central obesity is a requirement. Alternatively, the WHO definition[19] requires glucose intolerance, impaired glucose tolerance or diabetes and/or insulin resistance
- The American Association of Clinical Endocrinologists (AACE) and the European Group for the Study of Insulin Resistance (EGIR) have also developed diagnostic criteria for MetS (*Table 2*); however, both definitions are limited. The AACE definition[20] leaves the diagnosis to clinical judgment, with no set number of criteria required. The EGIR definition only applies to persons without diabetes mellitus[21].

Abdominal obesity, hypertension and hyperglycaemia are the most frequently occurring components of MetS[9]. MetS seems to be a graded condition, with the likelihood of sequelae, such as CVD and T2DM, increasing as the number of components of MetS increases[22]. Klein *et al.*[23] found that the presence of three MetS components* increases risk for CVD by 2.7 times compared with an increase of 5.9 times if four or more components are present. Even more strikingly, the presence of three MetS components increases the risk for T2DM by nearly 10-fold, whereas the presence of four or more components increases risk for T2DM by nearly 35 times. The occurrence of certain cancers has also been associated with MetS, but longitudinal studies linking the two are lacking[24].

OVERVIEW OF PERIODONTAL DISEASE

Periodontal disease is a group of conditions affecting the supporting tissues of the teeth – the gingiva, periodontal ligament, cementum and alveolar bone. It is most often the result of persistent infection and inflammation in response to the presence of periodontal pathogens (e.g. *Aggregatibacter actinomycetemcomitans*, *Porphyromonas gingivalis*, *Prevotella intermedia* and *Fusobacterium nucleatum*[25]). Gingivitis and periodontitis are the most common forms of periodontal disease. Gingivitis is an inflammation of the gingiva without loss of alveolar bone. It is plaque induced and can be reversed with improved oral hygiene. Gingivitis may develop into periodontitis, which is an inflammatory condition that results in loss of support for the dentition. Periodontitis is characterised by progressive and irreversible alveolar bone loss, and, ultimately, loosening and loss of teeth. Signs and symptoms include erythema, oedema and haemorrhage, deepening of the gingival crevice and periodontal pocket formation. Severe periodontitis is the sixth most prevalent disease in the world and the main cause of disability-adjusted life-years among oral conditions[26]. More than 47% of Americans ≥30 years of age have periodontal disease, with prevalence increasing to 70% among those ≥65 years of age. The condition is more common in men, those living below the poverty line and smokers[27].

Bacterial plaque/dental biofilm, microbial by-products, the host immune response, environmental and behavioural factors, and genetics contribute to the risk for periodontal disease[28]. The presence of periodontal pathogens is necessary, but not sufficient, to induce

Table 1 Diagnostic criteria for metabolic syndrome (MetS)

	WHO[19]	NCEP ATP III[16]	IDF[18]	AHA/NHLBI[17]
Required criteria	Dysglycemia and at least two other factors	Three or more of the following	Central obesity and at least two other factors	Three or more of the following
CO	W/H > 0.90 (M) or W/H > 0.85 (F) and/or BMI > 30 kg/m^2	WC > 40 inches (M) or WC > 35 inches (F)	Defined by WC*	WC ≥ 40 inches (M) or WC ≥ 35 inches (F)
TG	TG ≥ 150 mg/dL and/or HDLc < 35 mg/dL (M) or <39 mg/dL (F)†	≥150 mg/dL	≥150 mg/dL or drug treatment for elevated TG	≥150 mg/dL or drug treatment for elevated TG
HDLc		<40 mg/dL (M) or <50 mg/dL (F)	<40 mg/dL (M) or <50 mg/dL (F) or drug treatment for reduced HDLc	<40 mg/dL (M) or <50 mg/dL (F) or drug treatment for reduced HDLc
HTN	≥140/90 mmHg	≥130/85 mmHg	SBP ≥ 130 mm Hg or DBP ≥ 85 mmHg or antihypertensive drug treatment	SBP ≥ 130 mmHg or DBP ≥ 85 mmHg or antihypertensive drug treatment
Dysglycemia	Glucose intolerance, IGT or T2DM and/or IR	Fasting glucose ≥110 mg/dL	FPG ≥ 100 mg/dL or previous diagnosis of T2DM	Fasting glucose ≥ 100 mg/dL or drug treatment for hyperglycemia
Other	Microalbuminuria‡			

AHA/NHLBI, American Heart Association and National Heart, Lung, and Blood Institute; BMI, body mass index; CO, central obesity; DBP, diastolic blood pressure; F, female; FPG, fasting plasma glucose; HDLc, high-density-lipoprotein cholesterol; HTN, hypertension; IDF, International Diabetes Federation; IGT, impaired glucose tolerance; IR, insulin resistance; M, male; NCEP ATP III, National Cholesterol Education Program's Adult Treatment Panel III; SBP, systolic blood pressure; T2DM, type 2 diabetes mellitus; TG, triglycerides; WC, waist circumference; W/H, waist-to-hip ratio; WHO, World Health Organization.
*Variable according to sex and ethnic group.
†Hypertriglyceridemia and reduced HDLc fulfil the same criteria.
‡Defined as urinary albumin excretion rate ≥20 μg/min, or albumin:creatinine ratio ≥30 mg/g.

Table 2 Additional diagnostic criteria for metabolic syndrome (MetS)

	EGIR[21]	AACE[20]
Required criteria	Non-diabetic with IR or fasting hyperinsulinemia (highest quartile) and two or more of the following	No specific criteria required; diagnosis is left to clinical judgment based on the presence (or absence) of the following
Additional criteria	• FPG ≥ 6.1 mmol/L or IFG • BP ≥ 140/90 mmHg or antihypertensive drug treatment • TG ≥ 2.0 mmol/L or HDLc < 1.0 mmol/L or treatment for dyslipidemia • WC ≥ 94 cm (M) or ≥80 cm (F)	• Glucose intolerance (IFG or IGT) • Abnormal uric acid metabolism (plasma uric acid concentration or renal uric acid clearance) • Dyslipidemia (TG, HDLc, LDL-particle diameter, postprandial accumulation of TG-rich lipoproteins) • Haemodynamic changes (SNS activity, renal sodium retention, blood pressure) • Prothrombotic factors (PAI-1, fibrinogen) • Markers of inflammation (CRP, WBC, etc.) • Endothelial dysfunction (mononuclear cell adhesion, plasma concentration of cellular adhesion molecules, plasma concentration of asymmetric dimethylarginine, endothelial-dependent vasodilatation)

BP, blood pressure; CRP, C-reactive protein; F, female; FPG, fasting plasma glucose; HDLc, HDL cholesterol; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; IR, insulin resistance; LDL, low-density lipoprotein; M, male; PAI-1, plasminogen activator inhibitor-1; SNS, sympathetic nervous system; TG, triglycerides; WBC, white blood cells; WC, waist circumference.

periodontitis. In the physiological state, where there are no disease-modifying risk factors, the host responds appropriately to bacterial accumulations by attempting to restrict the bacterial infection. However, disease modifiers, such as smoking and diabetes mellitus, shift the immuno-inflammatory responses outside their normal physiological boundaries. Both humoral and cellular immune responses are also activated, but it is the inflammatory response that is believed to be responsible for the tissue destruction that characterises periodontitis. This exuberant inflammatory response and/or modified repair mechanisms leads to destruction of the periodontal tissues. Overall, it is postulated that the range of host responses (and clinical expressions) of periodontal disease are primarily determined by genetic and environmental factors[29].

Following excessive production of cytokines, ILs and other inflammatory mediators, the host response is

Table 3 Classification of chronic periodontitis[33]

Extent	Severity
Localised: ≤30% of sites involved Generalised: >30% of sites involved	Slight: 1–2 mm CAL Moderate: 3–4 mm CAL Severe: ≥5 mm CAL

CAL, clinical attachment loss.

responsible for loss of non-mineralised tissues of the periodontium, and crestal alveolar bone resorption. During bacterial challenge, neutrophils, macrophages, monocytes, mast cells and other cells of the innate immune system are recruited to the area. As well as responding to the bacterial infection, if these cells release additional cytokines, there is continued cell recruitment and activation of the complement system. Enhanced neutrophil recruitment can result in tissue destruction, and macrophages and a variety of other constituent cells (e.g. fibroblasts, endothelial cells) can also release inflammatory mediators, including matrix metalloproteinases (MMPs), which cause breakdown of extracellular matrix. Release of MMPs is also stimulated by prostaglandins [e.g. prostaglandin E_2 (PGE_2)], which are locally functioning hormones capable of inducing a wide range of responses[28]. TNF-α, PGE_2 and ILs (e.g. IL-1β, IL-6, IL-11 and IL-17) increase expression of receptor activator of nuclear factor kappa-B ligand (RANKL)[28,30,31]. When bound to its receptor, RANKL induces osteoclast differentiation and activity, leading to resorption of the crestal alveolar bone.

Periodontitis may be classified as chronic or aggressive. Chronic periodontitis is the most common form of the disease in adults and is usually characterised by slow-to-moderate progression (although periods of rapid progression are possible[32]). Chronic periodontitis is diagnosed according to the clinical signs of increased periodontal probing depth (PPD), clinical attachment loss (CAL), gingival inflammation and alveolar bone loss detectable on radiographs. The condition is further classified (*Table 3*) according to extent (localised or generalised) and severity (slight, moderate or severe[33]). For the purposes of population-based studies of periodontal disease, the two measurements most critical to diagnosis are PPD and CAL. The Centers for Disease Control and Prevention and American Academy of Periodontology (CDC/AAP) and the WHO are among the groups which have defined criteria for periodontal disease in populations (*Table 4*). While the CDC/AAP definition[34] is based on measurement of PPD and CAL, the WHO index[35] focuses on PPD, gingival inflammation (as measured by bleeding on probing) and the presence of calculus.

Despite efforts to define periodontitis, no universally accepted minimum definition currently exists. Studies often use modified versions of the CDC/AAP or WHO definitions of periodontitis (or other indices). The PPD or CAL measurements necessary to diagnose and classify periodontitis (i.e. severity) often differ from one study to another. Furthermore, there is variability between studies in the number of tooth sites, tooth surfaces and teeth that are examined.

EVIDENCE FOR A RELATIONSHIP BETWEEN PERIODONTAL DISEASE AND METABOLIC SYNDROME

Cross-sectional epidemiological studies have supported a potential relationship between periodontal disease and MetS (*Table 5*). Lee *et al.*[36] demonstrated a positive correlation between the number of MetS components and the presence of gingivitis in a population of 12- to 18-year-old individuals. In reference to periodontitis, D'Aiuto *et al.*[37] found an association between periodontitis severity and prevalence of MetS

Table 4 Criteria defining periodontal disease in populations

	CDC/AAP[34]		WHO[35]
	Severe periodontitis*	Moderate periodontitis*	
Definition	Two or more interproximal sites with CAL ≥ 6 mm (not on same tooth) AND one or more interproximal sites with PPD ≥ 5 mm	Two or more interproximal sites with CAL ≥ 4 mm (not on same tooth) OR two or more interproximal sites with PPD ≥ 5 mm (not on same tooth)	Using a graduated probe, each sextant of the mouth is given an index score according to the 'worst' finding observed in the sextant. A higher CPI code indicates more severe periodontal disease. CPI codes: 0: no PPD ≥ 3.5 mm 1: no PPD ≥ 3.5 mm but BOP 2: no PPD ≥ 3.5 mm but calculus present 3: PPD > 3.5 mm but < 5.5 mm 4: PPD ≥ 5.5 mm

BOP, bleeding on probing; CAL, clinical attachment loss; CDC/AAP, Centers for Disease Control and Prevention and American Academy of Periodontology; CPI, Community Periodontal Index; PPD, probing depth.
*No or mild periodontitis is defined by the absence of moderate or severe periodontitis.

Table 5 Associations between metabolic syndrome (MetS) and periodontal disease

Reference number	Study conclusions	Results/odds ratio
43	In a longitudinal study, MetS was a predictor of tooth loss and worsening periodontal disease in men. While the associations were slightly stronger according to the IDF criteria, evidence of a relationship between MetS and periodontal disease outcomes was also apparent according to NCEP ATP III criteria	As defined by IDF criteria, MetS increased hazard ratios for tooth loss (1.39), PPD ≥ 5 mm (1.37), CAL (1.19), alveolar bone loss (1.25) and tooth mobility ≥0.5 mm (1.43). As defined by NCEP ATP III criteria, MetS increased hazard ratios for tooth loss (1.44), PPD ≥ 5 mm (1.32) and tooth mobility (1.43). Hazard ratios of tooth loss and periodontal disease outcomes also increased per each additional positive MetS component
36	The number of positive MetS components was correlated with gingivitis in participants 12–18 years of age	OR: 1.92 (one MetS component) OR: 3.29 (three or more MetS components)
44	Individuals with longer durations of diabetes mellitus, hypertension and obesity, and/or a higher number of MetS components were more likely to have periodontal disease	OR: 3.82 (one MetS component) OR: 10.54 (more than two MetS components)
41	In a meta-analysis, those affected by MetS were nearly twice as likely to have periodontitis compared with those without MetS	OR: 1.7–2.1
38	Individuals with severe PPD (≥6 mm) and severe CAL (≥6 mm) and moderate PPD (4–5 mm) and moderate CAL (4-5 mm) had significantly higher risk for MetS	OR: 1.35 (severe PPD and CAL) OR: 1.25 (moderate PPD and CAL)
39	MetS was found to be significantly associated with periodontitis, in a dose–effect relationship	OR: 1.53 (three MetS components) OR: 2.20 (more than three MetS components)
45	A higher CPI code was associated with the presence of a higher number of MetS components	OR: 2.13 (three MetS components) OR: 2.34 (more than three MetS components)
46	Risk for more severe periodontal disease increased incrementally with the number of MetS components	OR: 1.8 (two MetS components) OR: 2.4 (three or four MetS components)
40	After adjusting for age, gender, education, toothbrushing, income, smoking and PI, the severity and extent of periodontal disease were significantly higher among patients with MetS compared with those without MetS	Compared with controls, those with MetS had significantly ($P < 0.0005$) higher GI, PPD, CAL, sites with CAL ≥ 3 mm and sites with PPD ≥ 3 mm
37	MetS has a prevalence of 18% in those with no/mild periodontitis but a prevalence of 37% in those with severe periodontitis (classified by clinical criteria of Page & Eke)	

CAL, clinical attachment loss; CPI, Community Periodontal Index; GI, gingival index; IDF, International Diabetes Federation; NCEP ATP III, National Cholesterol Education Program's Adult Treatment Panel III; OR, odds ratio; PI, plaque index; PPD, probing pocket depth.

in a US population. The prevalence of MetS was 18% in those with no/mild periodontitis compared with 37% in those with severe periodontitis. In adult Japanese subjects (34–77 years), those with severe PPD and severe CAL or moderate PPD and moderate CAL had significantly higher odds ratios (ORs) for MetS (1.35 and 1.25, respectively) compared with individuals without those periodontal conditions[38]. In a Korean population, Han *et al.*[39] reported that MetS was associated with periodontitis in individuals >44 years old, in male subjects and in smokers. Khader *et al.*[40] observed an association between MetS and the severity and extent of periodontal disease in a case–control study in northern Jordan.

In a meta-analysis, Nibali *et al.*[41] evaluated the evidence regarding the association between periodontal disease and MetS. Those affected by MetS were nearly twice as likely to have periodontitis (OR = 1.7–2.1) compared with those without MetS (*Table 5*). Nibali *et al.* emphasised that, despite their findings, it is unknown whether the presence of MetS, rather than the sum of its individual components, was the cause of the increased prevalence of periodontitis. One study[42] included in this meta-analysis was a 4-year cohort, which found that the risk for developing individual MetS components was higher in subjects with a Community Periodontal Index (CPI) code of ≥3 (OR = 1.6). The development of hypertension (OR = 1.5) and lipid abnormality [elevated TG or low HDL cholesterol (HDLc) levels; OR = 1.9] was associated with a CPI code of ≥3, but hyperglycaemia and obesity were not.

A separate longitudinal study of US males[43] found that MetS increased hazard ratios for tooth loss, PPD ≥ 5 mm, CAL ≥ 5 mm, alveolar bone loss ≥40% and tooth mobility ≥0.5 mm (*Table 5*). As part of this study, participants underwent periodic medical evaluations for up to 33 years. At baseline, the overall prevalence of MetS in participants was 44% according to IDF criteria and 37% according to NCEP ATP III criteria (*Table 1*). Hazard ratios for tooth loss and periodontal disease outcomes also increased with each additional MetS component, according to both IDF and NCEP ATP III criteria. While the associations were slightly stronger according to the IDF criteria, evidence of a relationship between MetS and periodontal disease outcomes was also apparent according to NCEP ATP III criteria. A number of other studies

demonstrate that the risk for periodontitis increases with the number of MetS components present in an individual[36,39,44–46].

Systemic oxidative stress is hypothesised as a potential link between periodontitis and MetS[15]. Increased cytokine concentration and oxidative stress as a result of periodontitis could lead to reduced insulin sensitivity. Decreased insulin sensitivity is considered a significant event in the development of MetS. Alternatively, the presence of MetS or one of its components could facilitate a pro-oxidant state with potential to diminish the antioxidant capacity of the periodontal tissues, thus impairing the normal physiological response to bacterial challenge and increasing the risk of periodontal disease. However, a critical review of the literature studying this association noted the heterogeneity in study design and the absence of many longitudinal studies. Age is an important confounding variable in the periodontal disease–MetS relationship[47].

Reports have examined the relationship of the individual conditions (dysglycemia, obesity, atherogenic dyslipidemia and hypertension) that are part of the MetS to the prevalence of periodontal disease, and this is discussed in the following sections.

Dysglycemia and periodontal disease

Of all the components of MetS, dysglycemia is the one with the most well-established relationship to periodontal disease. The postulated mechanism for the association is centred on formation of AGEs and persistent inflammation. In the persistent dysglycemic state, AGEs accumulate, resulting in increased oxidative stress in the periodontium, and AGE–RAGE interactions may increase expression of RANKL[48]. Expression of RANKL may be further increased as a result of the elevated levels of IL-1β, TNF-α and PGE_2 associated with diabetes[49]. In addition, compared with healthy subjects, persons with diabetes and severe periodontitis demonstrate reduced chemotaxis and phagocytosis, as well as altered superoxide production (as a measure of killing capacity) by polymorphonuclear leukocytes (PMNs)[7,50,51]. This allows PMNs with diminished function to accumulate in the periodontal tissues, resulting in an abscess-like condition.

Dysglycemia is associated with periodontal disease (*Table 6*). A study[52] that examined newly identified/previously untreated subjects with dysglycemia found that individuals with T2DM or pre-diabetes had a greater number of teeth with at least one PPD of ≥ 5 mm and a larger number of missing teeth, compared with subjects with normoglycemia. The differences in these measures were also significant between individuals with T2DM and pre-diabetes. Kwon *et al.*[53] observed that individuals with elevated fasting plasma glucose (FPG) had increased odds of periodontitis (OR = 1.43), and Morita *et al.*[46] showed that elevated FPG (OR = 1.9) and elevated glycated haemoglobin (HbA1c; OR = 2.0) increased the

Table 6 Associations between dysglycemia or obesity and periodontal disease

	Reference number	Study conclusions	Odds ratio
Dysglycemia	52	Individuals with T2DM or pre-diabetes were found to have more teeth with at least one PPD ≥ 5 mm ($P < 0.01$) and more missing teeth ($P < 0.01$) compared with those with normoglycemia	
	54	In both genders, those with periodontitis were more likely to have elevated FPG (≥110 mg/dL) compared with those with gingivitis or a healthy periodontium	1.61 (F) 1.13 (M)
	53	Elevated FPG (≥126 mg/dL) was shown to be the most important MetS component in association with periodontal disease, when adjusted for sociodemographic variables, oral and general health behaviours and oral health status	1.43
	55	After adjustment for confounders, insulin resistance (according to the HOMA index) was the only MetS component associated with severe periodontitis	3.97
	46	Elevated FPG (≥110 mg/dL) and elevated HbA1c (≥5.5%) were associated with the presence of periodontal pockets, when adjusted for age, gender and smoking	1.9 (FPG) 2.0 (HbA1c)
	37	Severe periodontitis (classified using the clinical criteria of Page & Eke) was associated with increased risk for elevated FPG (≥110 mg/dL)	1.71
Obesity	60	Those who were overweight or obese had increased risk for periodontitis	2.56 (OW) 3.11 (OB)
	62	In a systematic review and meta-analysis, it was shown that subjects who were overweight but not obese, obese, or overweight or obese, were more likely to have periodontitis than an individual of normal BMI	1.27 (OW) 1.81 (OB) 2.13 (OW or OB)
	61	In both genders, abdominal obesity was found to be the most important MetS component in association with periodontal disease	4.3 (F) 1.6 (M)
	63	Obesity was associated with increased risk for periodontitis, with the OR increasing with higher BMI	1.35
	46	Elevated BMI (≥25) was associated with the presence of periodontal pockets, when adjusted for age, gender and smoking	1.6

BMI, body mass index; F, female; FPG, fasting plasma glucose; HbA1c, glycated haemoglobin; HOMA, Homeostasis Model Assessment; M, male; MetS, metabolic syndrome; OB, obese; OW, overweight; PPD, probing depth; T2DM, type 2 diabetes mellitus.

likelihood of periodontitis. In a Taiwanese population, male (OR = 1.13) and female (OR = 1.61) subjects with periodontitis were more likely to be insulin resistant than were those with gingivitis or a healthy periodontium[54]. Similarly, D'Aiuto *et al.*[37] demonstrated an association between severe periodontitis and insulin resistance (OR = 1.74) in a US population, and Benguigui *et al.*[55] demonstrated that severe periodontitis was associated with insulin resistance (OR = 3.97) in an adult French population (35–74 years of age).

Obesity and periodontal disease

A systematic review investigating the relationship of being overweight or obese and periodontitis suggested that overweight, obesity, weight gain and increased waist circumference might all be risk factors for periodontitis[56]. The mechanism for the relationship is thought to involve TNF-α and IL-6, which are secreted from adipocytes and macrophages in the adipose tissue[57,58]. In the obese state, there is a marked increase in macrophage infiltration of adipose tissue[59]. As previously mentioned, TNF-α and IL-6 both increase osteoclast formation through up-regulation of RANKL expression. TNF-α also increases the host response to periodontal pathogens by recruitment of PMNs. Both TNF-α and IL-6 are believed to cause insulin resistance and stimulate production of acute-phase proteins [e.g. C-reactive protein (CRP)][7]. This can impact the ability of the periodontal tissues to respond appropriately to bacterial challenge, leading to enhanced tissue destruction.

Studies suggest that excess body weight increases the risk for periodontal disease, with the OR increasing with higher BMI (*Table 6*). Suvan *et al.*[60] found overweight (OR = 2.56) and obesity (OR = 3.11) to be associated with increased risk of periodontitis, while Morita *et al.*[46] found that a BMI of ≥ 25 increased the risk for periodontitis, albeit with a lower OR (1.6). In a cross-sectional study of US adults, MetS was associated with increased odds for periodontitis (OR = 1.6 in male subjects and OR = 4.3 in female subjects), with abdominal obesity being the largest contributing factor[61]. A systematic review and meta-analysis[62] showed that being overweight but not obese (OR = 1.27), obese (OR = 1.81) or either overweight or obese (OR = 2.13) increased the odds for periodontitis compared with an individual with normal BMI. Similarly, in a separate meta-analysis[63], obesity increased the risk for periodontitis (OR = 1.35), with the odds ratio increasing with higher BMI.

Atherogenic dyslipidemia and periodontal disease

Atherogenic dyslipidemia refers to elevated TG, variable low-density lipoprotein (LDL) cholesterol but increased smaller, cholesterol ester-depleted LDL and low HDLc, which may all contribute to atherosclerosis and risk of CVD. Elevated TG and reduced HDLc are components of MetS. Both of these markers of dyslipidemia have been associated with periodontitis (*Table 7*).

Elevated levels of TG were found to increase the odds for periodontitis (OR = 1.3), although not as significantly as were elevated levels of HbA1c, elevated fasting plasma glucose or BMI ≥ 25[46]. Tu *et al.*[54] found that periodontitis significantly increased the odds for elevated TG in both male and female

Table 7 Associations between atherogenic dyslipidemia or hypertension and periodontal disease

	Reference number	Study conclusions	Odds ratio
Atherogenic dyslipidemia	64	Low HDLc (<40 mg/dL M; <50 mg/dL F) was the only MetS component significantly associated with elevated serum antibody to *Porphyromonas gingivalis*, a marker of periodontal disease	2.96
	54	In both genders, those with periodontitis were more likely to have elevated TG (≥150 mg/dL)	1.32 (F) 1.12 (M)
	42	Over a 4-year time period, the development of atherogenic dyslipidemia was associated with a CPI code of ≥3	1.9
	61	In women, low HDLc (<50 mg/dL) increased risk for periodontal disease	2.0
	45	Low HDLc (<40 mg/dL M; <50 mg/dL F) was associated with a higher CPI code, when adjusted for age, gender and smoking	1.50
	46	Elevated TG (≥150 mg/dL) was associated with the presence of periodontal pockets, when adjusted for age, gender and smoking	1.3
Hypertension	42	Over a 4-year time period, the development of hypertension was associated with a CPI code of ≥3	1.5
	45	Hypertension (≥130 mmHg SBP or ≥85 mmHg DBP) was associated with a higher CPI code when adjusted for age, gender and smoking	1.59
	46	Hypertension (≥130 mmHg SBP or ≥85 mmHg DBP) was associated with the presence of periodontal pockets when adjusted for age, gender and smoking	1.2

CPI, Community Periodontal Index; DBP, diastolic blood pressure; F, female; HDLc, high-density lipoprotein cholesterol; M, male; MetS, metabolic syndrome; SBP, systolic blood pressure; TG, triglycerides.

subjects. In male subjects with periodontitis, the odds for elevated TG (OR = 1.12) were almost as high as those for insulin resistance (OR = 1.13). Low HDLc was associated with periodontitis in Japanese adults (OR = 1.50[45]) and in American female subjects (OR = 2.0[61]). Furthermore, a study of elderly Japanese subjects identified low HDLc as the only MetS component significantly associated with elevated serum antibody to *P. gingivalis* (OR = 2.96), a marker of infection associated with periodontal disease[64]. Nonetheless, other studies[37,55,65] failed to find a statistically significant association between periodontitis and either TG or low HDLc.

The comorbidity of atherogenic dyslipidemia and periodontitis is probably related to oxidative stress and chronic systemic inflammation, but the nature of this association remains under investigation[66]. It has also been suggested that periodontitis can increase potential for atherogenesis or cardiovascular events[67]. The proposed mechanism involves systemic inflammation, host response, development of a prothrombotic state or increased biosynthesis of cholesterol, secondary to the bacteraemia and systemic lipopolysaccharide (LPS) release characteristic of periodontitis. LPS and cytokines may also induce hypertriglyceridemia by stimulating TG production or inhibiting its clearance[68].

Hypertension and periodontal disease

Similarly to other MetS components, systemic inflammation, bacteremia, the host response and/or oxidative stress may all be implicated as possible associations between hypertension and periodontitis[69]. However, compared with the other MetS components, fewer studies show an association between hypertension and periodontitis (*Table 7*).

Amongst all MetS components, elevated blood pressure was associated with the greatest odds for a high CPI code (OR = 1.59) in a study of Japanese adults[45]. In contrast, Morita *et al.*[46] found hypertension as the MetS component that was least strongly associated with periodontal pockets (OR = 1.2), although the association was statistically significant. Other studies have not found a statistically significant association between hypertension and periodontitis[37,53,55,70].

CONCLUSION

The common thread between periodontal disease and MetS is oxidative stress. Oxidative stress leads to inflammation, and both individuals with MetS and individuals with periodontal disease show elevated levels of circulating inflammatory markers[7,66]. Chronic systemic inflammation may predispose an individual with periodontal disease to develop components of the MetS or vice versa. While the specific mechanisms of the relationship between MetS and periodontal disease are still under investigation, an association between the two conditions has been shown in cross-sectional studies and in a few longitudinal studies.

Dysglycemia and obesity are the components of the MetS that are most strongly associated with periodontal disease. There is good evidence for a bidirectional relationship between dysglycemia and periodontal disease[71,72]. Obesity leads to a persistent, low-grade inflammatory state, which can induce oxidative stress and ultimately periodontal tissue destruction. The potential for obesity to induce insulin resistance and dysglycemia provides further rationale for its relationship with periodontal disease.

Atherogenic dyslipidemia and hypertension demonstrate weaker associations with periodontal disease. As the number of MetS components present tended to increase the odds of periodontal disease, it is possible that atherogenic dyslipidemia and hypertension have an additive effect on risk, but only in the presence of dysglycemia and/or obesity. Evidence from one cohort study[42] suggests that the development of atherogenic dyslipidemia and hypertension may be related to the presence of periodontal pockets. This finding is supported by the hypothesis that the development of these two conditions may be secondary to systemic inflammation and/or oxidative stress caused by bacteraemia and systemic LPS release experienced by individuals with periodontitis[67,69].

It is unclear whether the relationship between MetS and periodontal disease is uni- or bidirectional. As shown in multiple studies, the odds for periodontitis increased with the number of MetS components present in an individual. However, as the overwhelming majority of studies investigating this relationship were of cross-sectional design, temporality and causality cannot be established. Longitudinal studies are needed to conclusively determine the direction of this relationship and to examine the possibility that MetS and periodontal disease are both part of an 'inflammatory phenotype'.

In addition to cross-sectional design, studies were also limited by population-based data, confounding factors and the lack of unified diagnostic criteria for both MetS and periodontal disease. Many studies evaluated specific populations and therefore the results may not be generalisable to other groups. Additionally, confounding factors, such as oral hygiene habits, socio-economic status, smoking, age and gender, probably impacted the results. For example, obese individuals may practice less healthy lifestyle behaviours (e.g. less frequent toothbrushing and a lower level of physical activity) than those who are of normal weight, which could also impact the odds for periodontitis. Many

studies adjusted for these and other confounders, but variability exists. Finally, while many studies used the revised NCEP ATP III criteria for the diagnosis of MetS, the criteria used to identify the presence of periodontal disease, and its severity, were inconsistent. Establishing unified diagnostic criteria for MetS and periodontal disease are essential to improve the understanding of this association.

Identifying a relationship between MetS and periodontal disease offers some potentially important clinical benefits. Some evidence suggests that non-surgical periodontal therapy reduces the levels of inflammatory mediators in serum[73,74]. If a clear relationship was established, treatment of early periodontal disease could be part of a treatment approach for MetS, and oral health providers could also refer at-risk patients for an evaluation for MetS, an important risk factor for chronic diseases[24,42]. Conversely, physicians would work with dentists to ensure that patients diagnosed with MetS receive a dental evaluation and treatment when dental disease is present. Together, these actions could improve both oral and general health outcomes.

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Competing interest

There are no competing interests.

NOTE

* The following six considered: hyperglycaemia (glucose ≥ 140 mg/dL or ≥ 7% glycated haemoglobin); hypertension (≥ 160/90 mmHg); high-risk lipid levels [serum total cholesterol level 2,265,200 mg/dL; or serum HDL cholesterol <35 mg/dL (male subjects) or <39 mg/dL (female subjects); or total cholesterol/HDL cholesterol >5.7 (male subjects) or >5.1 (female subjects)]; elevated BMI (>30 kg/m^2); elevated uric acid (>7.0 mg/dL); or proteinuria (≥30 mg/dL).

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